Chemistry Manufacturing and Controls

CBER 101

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CBER, US FDA

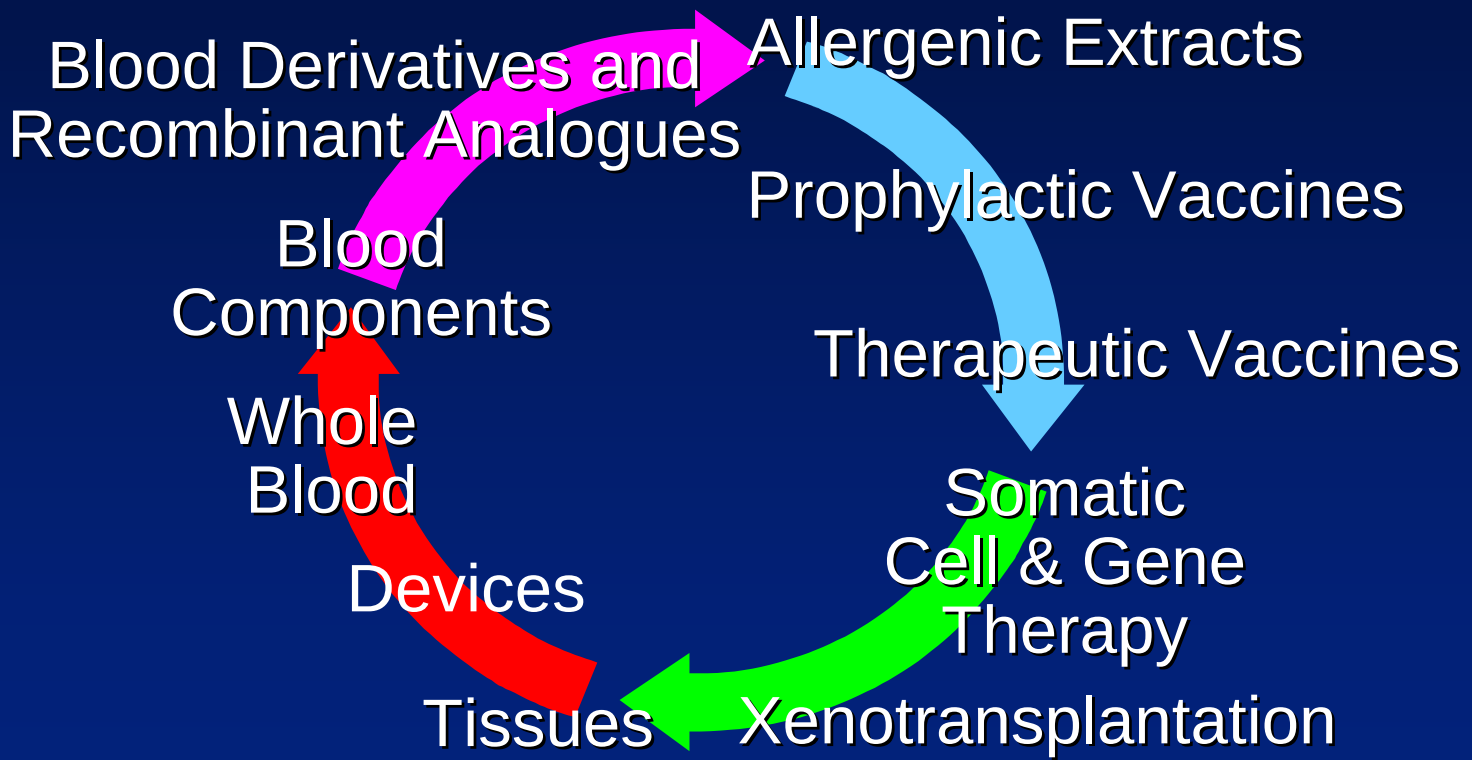
Overview

- Reviewer's Responsibilities
- Product Considerations
- IND Phase 1
- IND Development - Phase 2 & 3
- BLA Issues, Format & Content
- *Considerations*
- Post-Approval Changes
- Comparability
- Contract Manufacturing
- Acknowledgements/ Contacts
- References

CMC Reviewer - Major Responsibilities

- WHO -
  - Reviewer or researcher/ reviewer
  - Background
    - Biologists, Chemists/Biochemists, Microbiologists, Immunologist & Others
    - Variety of expertise
- WHERE -
  - OCGT, OBRR, OVRR, OCBQ (DMPQ)
- WHAT -
  - Review of CMC information submitted in IND, IDE, BLA
  - Review of “CMC-related information” in IND, IDE, BLA
  - Review of CMC information on facility inspection
  - CMC reviewer chairs BLA Review Committee (for new biologics, manufacturing supplement)

Biologics Regulated by CBER



Major Considerations For Biological Products

Parameter	Considerations
Manufacturing	Living sources Complex process Sensitive to change & Environmental influences Large amount of variability
Contaminants	Subject to contamination Viral/bacteria/fungal/TSE Agent
Structure Active Ingredient	Multiple molecular species Heterogeneous

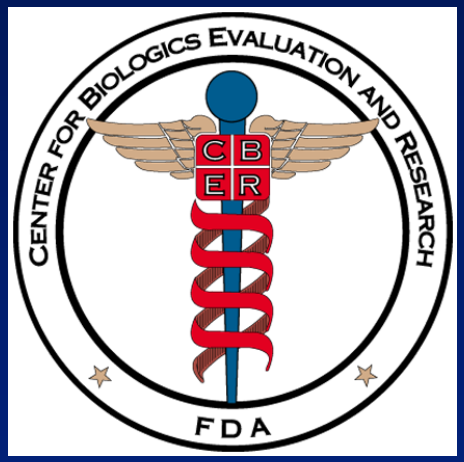
Major Considerations For Biological Products

Parameter	Considerations
Impurities	Difficult to define and quantitative
Characterization (methods of analysis)	Limitations activity/cont/impurities

Implications for CMC

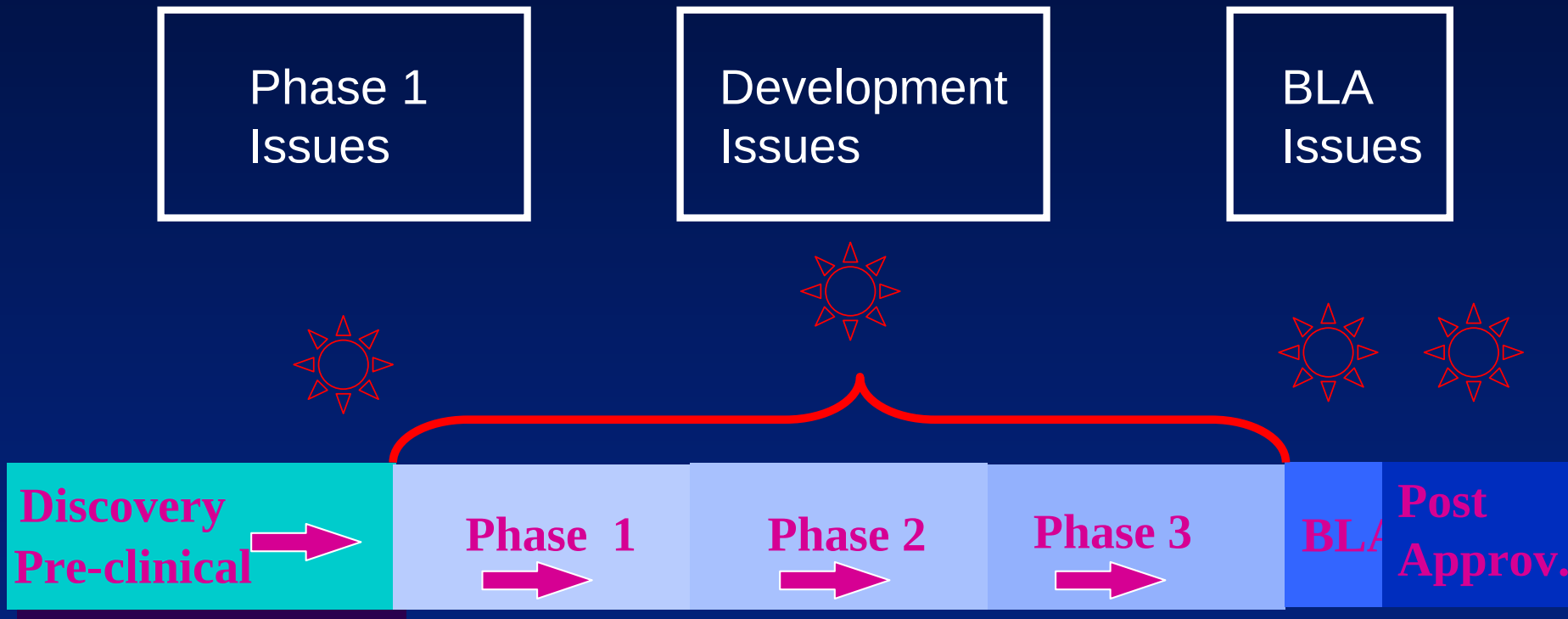
- Requires thorough description, characterization, and controls starting with source material
- Description and evaluation of manufacturing changes during development for potential product impact
  - Difficult to distinguish quality change that can impact safety
  - Product Comparability
- Greater reliance on process control & process validation
- Greater emphasis on the Drug Substance
- Some “cGMP” information is submitted and reviewed in context with other information submitted in the IND & BLA

Product Development and Regulation - CBER Philosophy



- Regulation Goal: Balanced, Flexible, Responsive
  - » Assure the safety and rights of subjects
  - » Protect the public health
  - » Not impede technological innovation & product development
- Influences
  - » Available scientific knowledge, pre-clinical, clinical knowledge & experience
  - » Scientific Research
  - » Crises/ tragic events
- Appropriate Risk Assessment

Product Lifecycle



General Principles

"The amount of information on a particular drug that must be submitted in an IND to assure the accomplishments of the objectives… *{safety & quality}* …depends upon such factors as the novelty of the drug, the extent to which it has been studied previously, the known or suspected risks and the developmental phase of the drug." [21 CFR, 312.22(b)]

General Principles

“ Although in each phase of the investigation sufficient information is required to be submitted to assure the proper identification, quality, purity, and strength of the investigational drug, the amount of information needed to make that assurance will vary with the phase of the investigation, the dosage form, and the amount of information otherwise available.” [21 CFR 312.23 (a)(7)(i)]

Phase 1

General Principles

"FDA's primary objectives in reviewing an IND are, in all phase of the investigation, to assure the safety and rights of subjects, … FDA's review of Phase 1 submissions will focus on assessing the safety of Phase 1 investigations…, [21 CFR, 312.22(a)]

Phase 1 Considerations

- CMC safety issues as they relate to quality aspects
- What is the risk for human subjects? Are there any signals?
- Product class and individual products affect, to some extent, the type and extent of information needed to assess safety
- How some information is reported may influence the type and extent of other information that should be provided
- Unique issues associated with specific products
  - Known labile product
  - Substantial time elapsed from manufacture and testing

Viral Safety of Biologicals

Potential Viral Contamination

- Biological Source Material
- Contaminated Raw Materials
- Adventitiously introduced In manufacturing

Approaches (Prevention & Elimination)

- Selection
- Testing
- Clearance
- cGMP's

Biological Source Material

- Evaluation
  - Risk assessment of parent cells - history, potential exposure to viral agents
  - Screening plasma donors for risk factors
- Testing for viruses
  - Donors, animals, host cells, cell banks, EPC
  - General and Species specific tests
- Control
  - Establishing & maintaining cell banks under cGMP's
  - Establishing plasma donor deferral roles for unsuitable donors
  - Closed herds & flocks, sentinel animals
  - Quarantine until testing and control assures and establishe safety

Materials

- Qualification of materials
  - Raw materials & excipients
  - Animal and human origin
  - Appropriate screening, testing – source & material dependent
  - Specialized reagents – may require Viral Clearance Evaluation Studies
- Elimination of human and animal materials
- Pre-treatment for potential contaminating viruses

Manufacture

- Testing for viruses at appropriate production stage
  - In-process
    - Unpurified cell culture harvests, milk
    - Adventitious Agents
    - Known endogenous viruses (e.g., EBV)
  - Drug Product (Final Container Testing)
- Viral Clearance Evaluation/Validation Studies
- Adherence to cGMP's

CMC Content - Phase 1

- Description of the manufacturing process - Drug Substance & Drug Product
  - Method of preparation, including:
    - complete description covering source, expression methods, materials and components, culture, purification, formulation, finishing, storage periods and conditions
    - establish safety-related acceptance criteria – (e.g., critical components, ancillary products, lot release DS/DP)
    - description of differences in manufacturing for DS & DP for clinical studies versus preclinical studies
  - Adequate description of process controls for process steps that affect safety (e.g., virus inactivation, vaccine attenuati aseptic filling)

CMC Content - Phase 1

- Source origination & characterization (animals, humans, cell lines, cell banks, viral seeds)
- Appropriate description of the Drug Substance
  - Characterization information (structural, physiochemical, immunological)
- Appropriate testing
  - Description of tests, analytical procedures & acceptance criteria
    - safety testing throughout process
    - DS & DP release testing (i.e., identity, purity, potency, strength)
    - testing results on preliminary/ available lots (e.g., toxicological studies to be used in clinical studies)

CMC Content - Phase 1

- Endogenous virus testing
- Prevention and control of contamination by adventitious microbial agents (viruses, bacteria, fungi, mycoplasma) & TSE agents
  - Source Screening/ Testing
  - Raw materials of human or animal origin
  - Testing at appropriate stages of production
  - Demonstrated clearance (inactivation/removal) for viruses
  - Control through appropriate cGMP's

CMC Content - Phase 1

- Ruminant-derived materials (e.g., bovine origin)
  - Assure material from BSE-free country [USDA 9 CFR 94.18]
  - Identify country of origin & tissue source in submission
  - Maintain traceable records
  - Also test for viral agents [e.g., 9 CFR]
  - Emphasis on risk assessment

CMC Content - Phase 1

- Information to support stability during toxicological studies and planned clinical study
  - Description of stability testing
  - Preliminary/ available stability test results
  - Establish a real – time stability protocol
  - Perform accelerated stability (Phase 2/ 3)

Testing - Sterility

- Sterility of the Cell Banks, Product, and Placebo must be demonstrated by testing for viable organisms (bacteria & fungi)
- Recommend following 21CFR 610.12
- Newer Methods
- What about short-lived biologics, other situations (e.g., cell therapies)?

Testing - Sterility (cont.)

- Possible exceptions for cell therapies, tissues, & short-lived radiopharmaceuticals (discuss options with CBER):
- Cell therapies
  - » Gram-stain/ Follow-up with culture test
  - » Action plan-based upon subsequent positive contamination in sterility test after cell administration
    - – `Patient/physician notification, investigation, speciation
- Process validation - cell therapies & other biologics

Testing - Mycoplasma

- Test for culturable and non-culturable
- Recommend 21 CFR 610.30 for culture test
- Options for non-culture test:
  - Hoechst stain
  - PCR
  - Newer methods

Testing Endotoxin (pyrogenicity)

- Options
  - Rabbit-pyrogenicity test (21CFR 610.13(b)) or
  - Limulus Amebocyte Lysate (LAL) test

- Acceptable levels (LAL)
  - 5 Endotoxin units (EU) per kg body weight per hour for parenteral administration
  - 0.2 EU per kg body weight per hour for intrathecal administration

cGMPs in Development

- Elements of cGMP's need to be in place for manufacture of clinical materials used in Phase 1 including:
  - Personnel training
  - Written procedures, & documentation that allow for reproducibility, and traceability
  - "Quality Unit" oversight
  - Validation/ qualification of critical safety-related processes (e.g., Virus Attenuation/ Toxin inactivation)
  - Multiproduct manufacturing considerations
  - Appropriate facilities, change control procedures
  - Laboratory controls
- cGMPs develop with process and resulting product
- Control is expected to increase as development

Recent Examples of “cGMP” Information Submitted in IND

- Gene Therapy
  - Description of an adequate QA/QC program in place
  - Description of segregation and cleaning procedures to prevent cross-contamination from production of multiple GT vectors in the same facility
- Cellular Therapy
  - Description of tracking & segregation procedures for autologous cells to assure patient receives correct cells

IND Clinical Hold

"Human subjects are or would be exposed to an unreasonable and significant risk of illness or injury." [21 CFR 312.42 (b) (1) (i)]

"The IND does not contain sufficient information required under 312.23 to assess the risks to subjects of the proposed studies." [21 CFR 312.42 (b) (1) (iv)]

IND Development (Phase 2 & 3)

Development Goal

- GOAL: Licensing a Biologic Product
- CMC GOAL: Developing an established manufacturing process assuring consistent production of a quality product.
- Demonstrating comparability for manufacturing changes
  - Careful attention is required to evaluate changes made during development
  - Comparability changes post/during pivotal trial
- Establishing the relationship between DS and DP used in clinical studies (especially pivotal studies - phase 3) and the quality characteristics and attributes of the DS and DP to be approved

Development of CMC Information

Safety Information

Source characterization

Raw materials qual.

DS/DP Characterization

Testing or clearance of impurities, contaminants

Des. of manf. process

Process control esp. for safety processes (e.g., virus clearance)

Development

DS & DP Characterization

Assay Development (Reference standards Validation)

Stability

Specifications

Manf. Process Optimization (Control & Validation)

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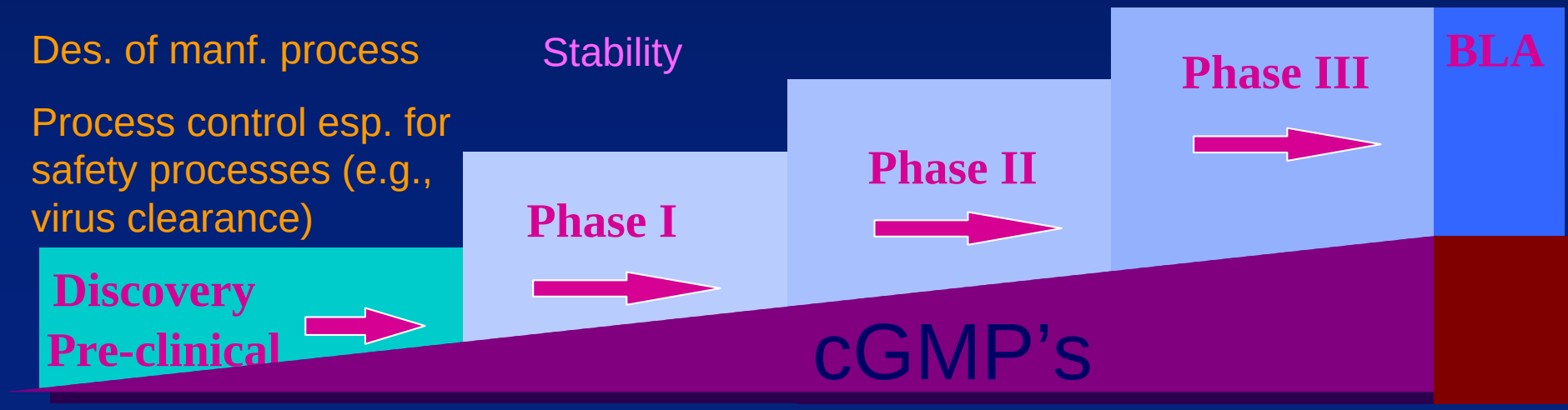


Analytical Methods Validation

- "Methods validation is the process of demonstrating that analytical procedures are suitable for their intended use." [FDA Draft Guidance on Analytical Procedures…]
- Analytical procedure:

  Does what it is intended to do
  Yields data to answer a question
  Provides confidence in the results

Analytical Methods Validation

- Although this guidance does not specifically address the submission of analytical procedures and validation data for raw materials, intermediates, excipients, container closure components, and other materials used in the production of drug substances and drug products, validated analytical procedures should be used to analyze these materials" **[FDA Draft Guidance Analytical Procedures…]**

- "In general, validated analytical should be used, irrespective of whether they are for in-process, release, acceptance or stability testing." **[FDA Draft Guidance Analytical Procedures…]**

Expectations For Analytical Methods During Development

- Ensure safety of the product
- Assurance that analytical information gained in development can be reliability related to commercial manufacturing
- Provides sufficient foundation for validation, specification, limits etc., by submission of marketing application

Analytical Method Validation

- Methods used in IND studies should be:
  - Scientifically sound, yield reproducible results and have sufficient sensitivity, specificity, and accuracy for the specified purpose.
  - Conducted following established written procedures under controlled conditions that may include use of reference materials, standards, positive, and negative controls or other appropriate controls.
- Compendial assays – assure performance (e.g., interference with test article)
- For pivotal investigational trials – validation should be strongly considered, may be needed for some assays

Process Validation

- Assures control of the process
  - minimize product failures
  - meets cGMP
- Assures consistent product quality
  - assessment of product attributes not measured on each batch
  - product will meet specification
  - suitable for its intended use

Process Validation Program

Source/starting materia characterization

Raw materials qualification

Evaluation studies for clearance of viruses/ impurities-control of production scale

Vaccine/toxin inactivation on production scale

Development Studies

Equipment
IQ, OQ, PQ

Conformance Lots – "validation study"

Materials qualification

Analytical Methods and Assay Qualification

Product Characterization

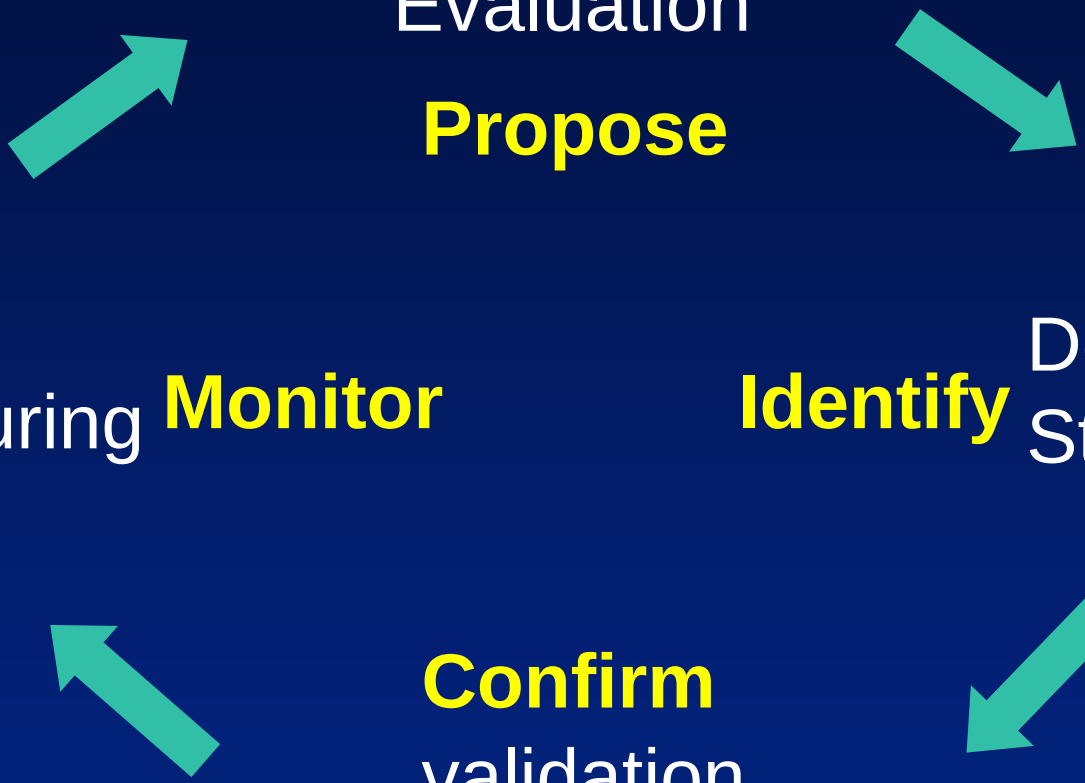
Accumulated manufacturing experience

"Validated Process"

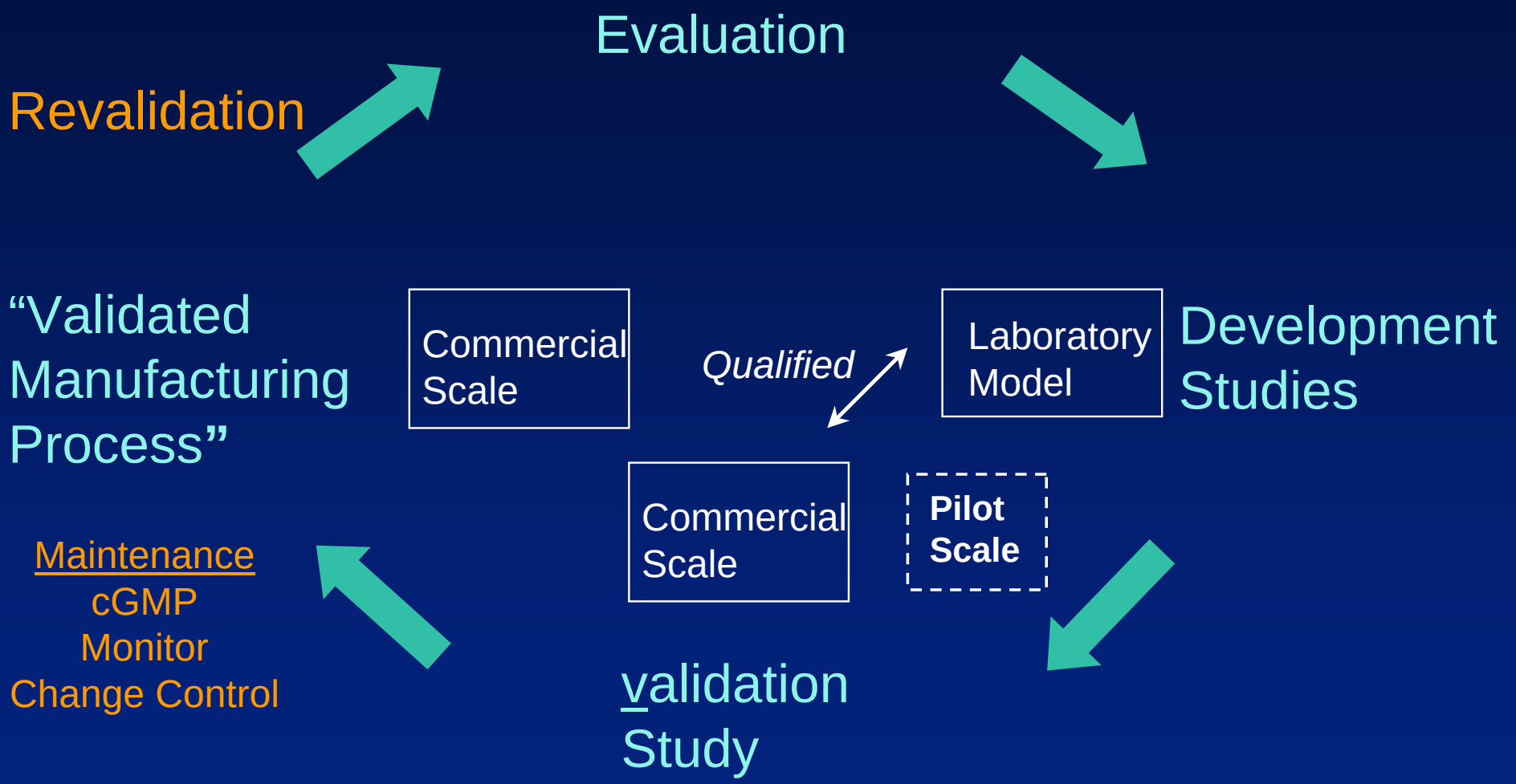
Change Control
Monitoring/Trendin
(Statistical Process
Control PC)

Discovery Pre-clinical | **Clinical (IND)** | **BLA** | **Post-Approval**

Validation Life Cycle



Validation Life Cycle



Phase 2 & 3

- Manufacturing Changes
- Lot-to-lot consistency
- Progressive Process Validation
- Progressive Analytical Methods Validation
- Refining Specifications

Manufacturing Changes

- Document the changes in an amendment.
- Describe the new method (highlight differences)
- Explain the reasons for implementing the change
- Perform side-by-side analyses to compare the “new” with the “old”.
- Consider potential impact on safety (e.g.,Need to perform viral clearance studies)
- Keep retention samples!!!

BLA Issues, Content, Format

Assuring Product Control & Quality

PROCESS

Source/ Raw materials testing

In-process Testing

Validation

cGMPs

PRODUCT

Characterization

Specifications

Release Testing

Stability Testing

Applicable Regulations

- Part 600 Establishment Standards, Establishment Inspection, Reporting of Adverse Experiences
- Part 601 Licensing
- 21 CFR 601.2 Applications for Biologics Licenses
  - "To obtain a biological license under section 351 of the PHS Act for any biological product…"
  - "…manufacturer shall submit an application to the Director, CBER…"
  - "…data meet the prescribed requirements of safety, purity, potency…"
  - "… full description of the manufacturing method;data establishing stability of the product throughout the dating period; samples representative of the product…"summaries of the results of tests performed on the submitted samples…

Applicable Regulations

- “Approval of BLA application or issuance of a biologics license shall constituent a determination that the establishment and the product meets applicable requirements too ensure continued safety, purity and potency of the product”
- Establishments meet applicable GMP requirements 21 CFR 210, 211, 600, 606, 820

- 21 CFR 610. General Biological Standards
  - Tests for sterility, potency, identity, purity, product specific tests
  - 21 CFR 610.2 Lot Release

Applicable Regulations

- Additional standards for product specific classes
  - Part 640 - human blood and blood products
  - Part 660 - diagnostic substances of laboratory tests
  - Part 680 - miscellaneous products
- "Specified Products" exempt from select establishment standards and some general biological standards

CMC Guidance

"WHAT" "HOW"

ICH "Technical Guidance"
FDA "Technical Guidance"

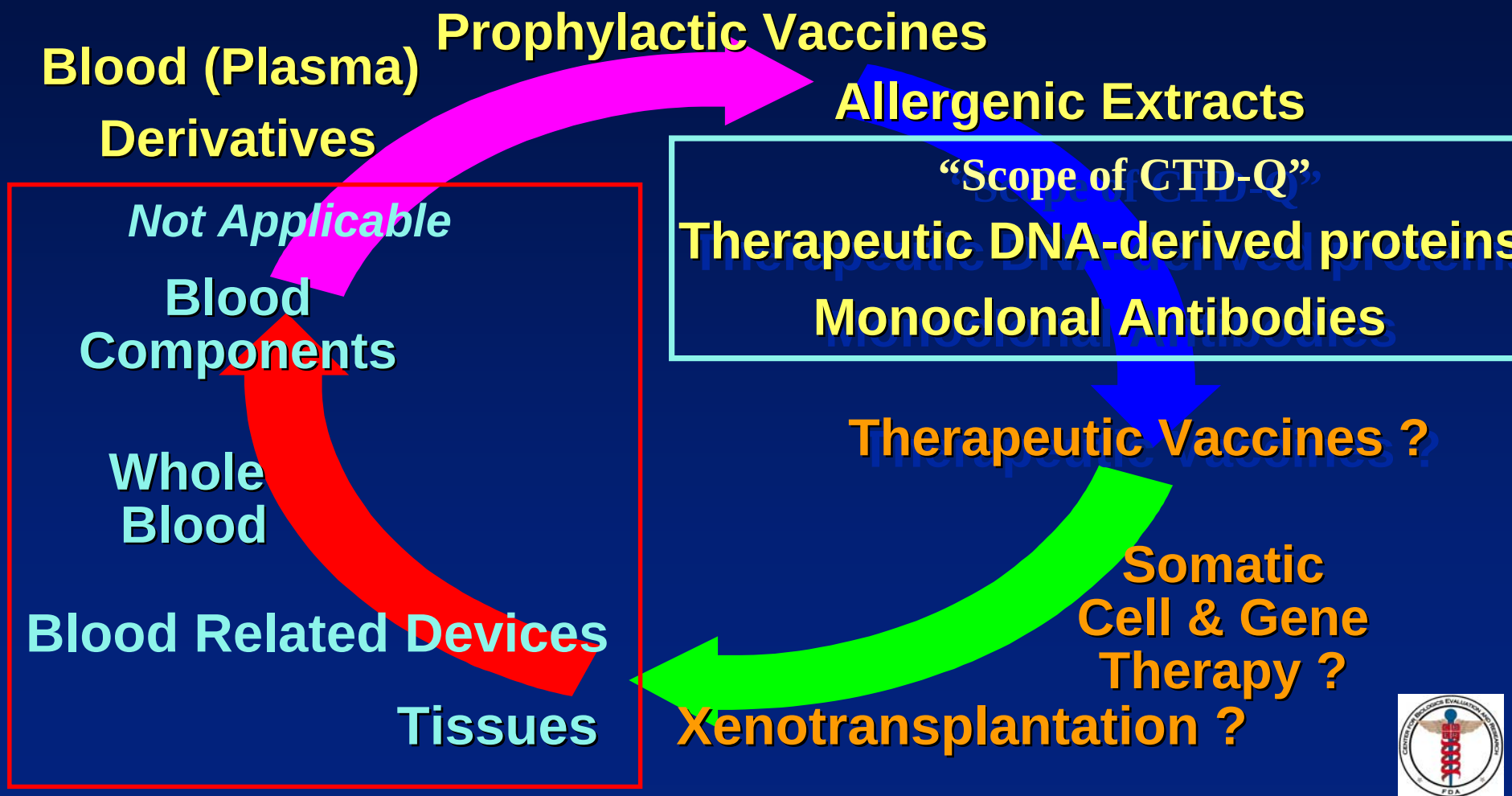
"WHERE"

Common Technical Document-Quality & FDA guidance

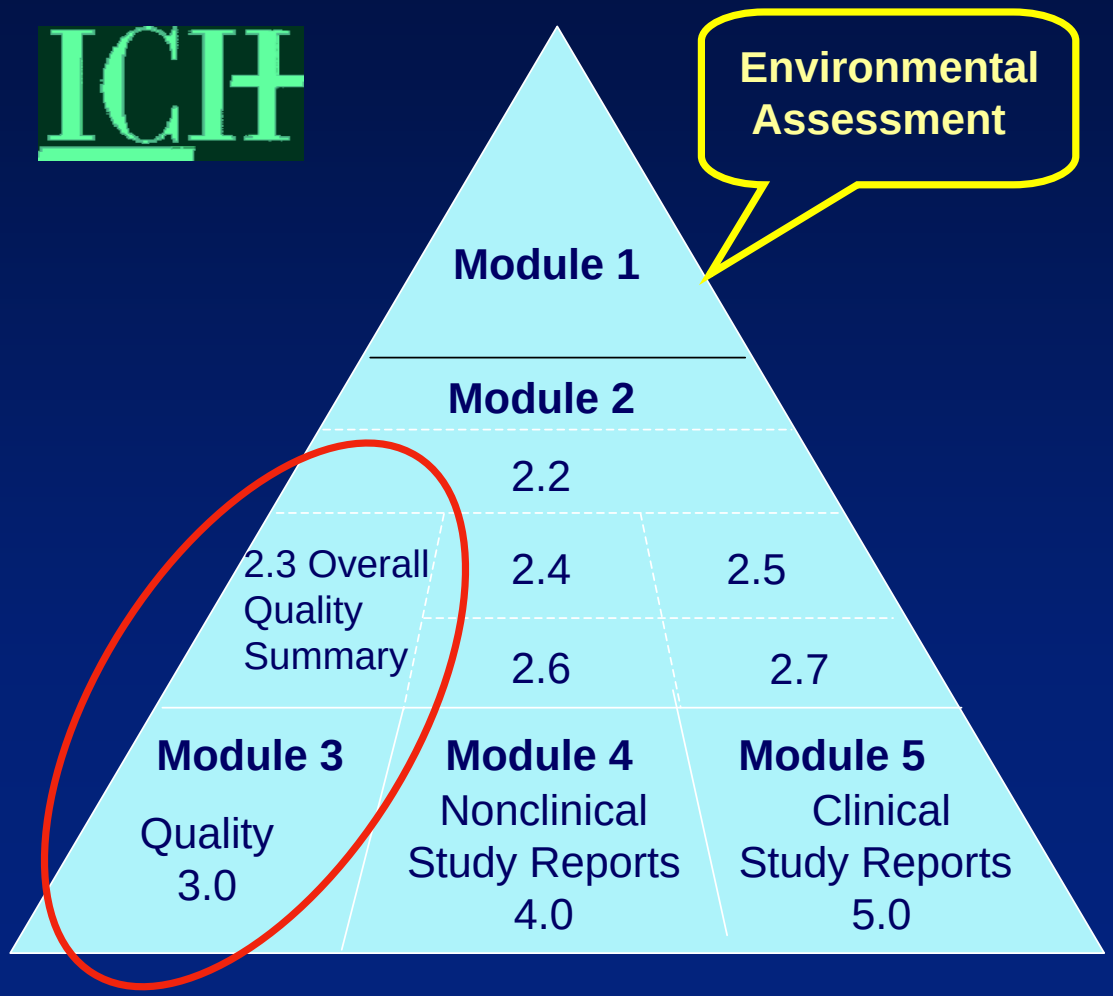
"WHERE & HOW

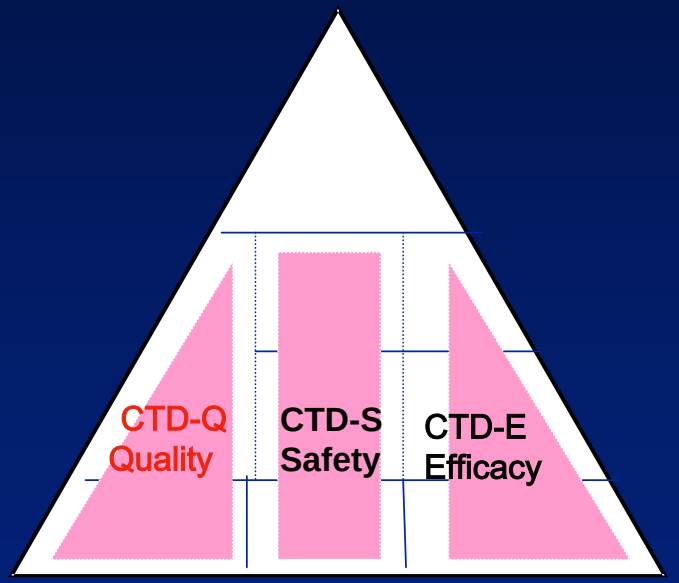
FDA Submission CMC Information Content & Format– *Product Class*

Applicability of CTD Format



Common Technical Document





Module 2.3: Quality Overall Summary

- An overview - written summary following the outline and scope of the Body of Data (Module 3)
- Critical key parameters of the product should be discussed
- No new information should be included that is not contained in Module 3
  - Most of the information including tables and figures can be imported directly from Module 3

Module 2.3: Quality Overall Summary

- Non-Clinical and Clinical Overviews:
  - contain a discussion and justification on the risk/benefit of the product;
- Quality Overall Summary:
  - it is a true summary
  - the justification is already included in the “Body of Data” (Module 3)

Overview of CTD Module 3

- 3.1 Module 3 Table of Contents
- 3.2 Body of Data
  - 3.2.S Drug Substance
  - 3.2.P Drug Product
  - 3.2.A Appendices
  - 3.2.R Regional
- 3.3 Literature References

3.2.S Drug Substance

- 3.2.S.1 General Information
- 3.2.S.2 Manufacture
- 3.2.S.3 Characterization
- 3.2.S.4 Control of Drug Substance
- 3.2.S.5 Reference Standards or Materials
- 3.2.S.6 Container Closure System
- 3.2.S.7 Stability

3.2.S.2 Manufacture

- 3.2.S.2.1 Manufacturers
- 3.2.S.2.2 Description of the Manufacturing Process and Process Controls
- 3.2.S.2.3 Control of Materials
- 3.2.S.2.4 Control of Critical Steps and Intermediates
- 3.2.S.2.5 Process Validation and/or Evaluation
- 3.2.S.2.6 Manufacturing Process Development

3.2.S.2 Manufacturing

- 3.2.S.2.2 Description of the Manufacturing Process and Process Controls
  - Description of entire process
  - Description of pooling, reprocessing
  - Focus on critical and noncritical processes, procedures and controls
  - Reference to other sections with additional detail

3.2.S.2 Manufacturing

- 3.2.S.2.3 Control of Materials
  - Information on all raw materials and components
    - Information to substantiate appropriate quality and suitability for use
  - Control of Source/Starting Materials
    - Master & Working Cell/ Seeds Banks, Source Plasma (Donor Testing)
    - Description, characterization and stability
    - Description and analysis of genetic construct

3.2.S.2 Manufacturing

- 3.2.S.2.4 Control of Critical Steps and Intermediates
  - Identification of critical process controls, acceptance criteria/ limits with supporting data
  - Information on all intermediates
- 3.2.S.2.5 Process Validation and/or Evaluation - Biotech
  - Information on validation of critical steps
    - Propagation/ Fermentation, Harvest, Purification
    - Revalidation studies as a result of process/scale changes
    - Aseptic Processing
    - Microbiology steps

3.2.S.2 Manufacturing

- 3.2.S.2.6 Manufacturing Process Development
  - Description of process development
  - Assessment of potential for change(s) to impact the Drug Substance
  - Comparative analytical studies of pre/post change
  - Comparability assessment

Comparability

- Demonstrate product comparability between a biological product made after a manufacturing change and a product made before implementation of the change
- “FDA may determine that two products are comparable if the results of comparability testing demonstrate that the manufacturing change does not affect safety, identity, purity or potency.”
- Comparability during development is often assessed as part of the clinical study
- FDA Guidance Concerning Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-derived Products [April, 1996]

3.2.S.3 Characterization

- 3.2.S.3.1 Elucidation of Structure and Other Characteristics
  - Specified Products
    - Desired Product
    - Product-related substances,
- 3.2.S.3.2 Impurities
  - Process-related impurities
  - Product-related impurities

3.2.S.4 Control of Drug Substance

- 3.2.S.4.1 Specification
- 3.2.S.4.2 Analytical Procedures
- 3.2.S.4.3 Validation of Analytical Procedures
- 3.2.S.4.4 Batch Analyses
- 3.2.S.4.5 Justification of Specification

3.2.S.7 Stability

- Information and data on real time, accelerated, and stress stability studies
- Post Approval Stability Protocol and Stability Commitments

3.2.P Drug Product

- 3.2.P.1 Description and Composition of the Drug Product
- 3.2.P.2 Pharmaceutical Development
- 3.2.P.3 Manufacture
- 3.2.P.4 Control of Excipients
- 3.2.P.5 Control of Drug Product
- 3.2.P.6 Reference Standards or Materials
- 3.2.P.7 Container Closure System
- 3.2.P.8 Stability

Pharmaceutical Development

(CTD-Q Definition)

- Information on the development studies conducted to establish that the dosage form, the formulation, manufacturing process, container closure system, microbiological attributes and usage instructions are appropriate for the purpose specified in the application.
- Additional, this section should identify and describe the formulation and process attributes (critical parameters) that can influence batch reproducibility, product performance and drug product quality

3.2.P.2 Pharmaceutical Development

- 3.2.P.2.1 Components of the Drug Product
- 3.2.P.2.2 Drug Product
- 3.2.P.2.3 Manufacturing Process Development
- 3.2.P.2.4 Container Closure System
- 3.2.P.2.5 Microbiological Attributes
- 3.2.P.2.6 Compatibility

3.2.A Appendices

- 3.2.A.1 Facilities and Equipment
- 3.2.A.2 Adventitious Agents Safety Evaluation
- 3.2.A.3 Novel Excipients

3.2.A.1 Facilities and Equipment

- Elimination of Establishment Licensing Application
- The manufacturing process includes facilities and equipment
- This information is reviewed in context with other information in the application. Other aspects also reviewed on inspection
- Type and extent of information will vary with the product class – covered in inspection presentation

3.2.A.2 Adventitious Agents Safety Evaluation

- Single compendium of all studies assessing the safety of the drug substance and drug product from *contamination* with adventitious agents
- Viral & non-viral (bacteria, mycoplasma, fungi, TSE agents)
- Overall picture for assessors.
- Collates information that would be spread throughout the BLA.
- ICH guidance for technical requirements [Q5A, Q5D]

3.2.R Regional Information

- 3.2.R Regional Information
  - Executed Batch Record (USA Only)
  - Comparability Protocols (USA Only)

Other Considerations

BLA Speed Bumps

- Demonstrating Product Comparability
- Process Validation Studies
- Setting Specifications
- Stability Studies
- Demonstrating Consistent Manufacture

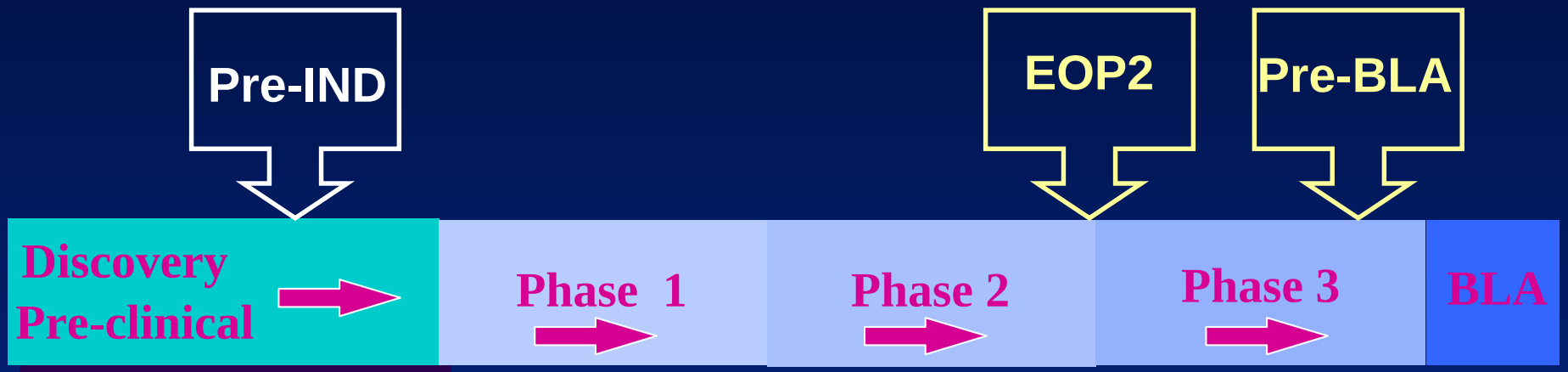
Impact of Accelerated Product Development

- Process validation - correctly established operating and performance parameters and limits?
- An accurate measure of manufacturing variability?
- Able to establish and meet limits and specifications - manufacturing consistency?
- Greater reliance on
  - Post-approval manufacturing history and experience to "confirm" specifications & limits
  - Approval Commitment - to reevaluate, specifications/ limits based upon additional manufacturing experience

Post Approval Commitments

- Outstanding issues that cannot be resolved prior to approval of application – not impinge on approvability, product safety
- Discussed during review
- Specified in approval letter with submission time commitment

Proper Planning – Utilize IND Meetings*



*Other meetings possible (e.g., Fast track, Phase 3 follow-up)

Post-Approval

Changes to an Approved Application

(21 CFR 601.12, July 24, 1997)

- FDAMA Section 116
- Changes to an approved application
  - product, production process, quality control, equipment, testing, facilities, labeling
- Potential for change to have an adverse effect on a products identity, strength, quality, purity, or potency as they may relate to its safety or effectiveness.
- Potential determines reporting categories

Post Approval Reporting Categories

- Prior Approval Supplement (PAS)
  - substantial potential
  - Distribute product - upon supplement approval
- Changes Being Effected - 30 days (CBE-30)
  - moderate potential
  - Distribute product 30 days after supplement receipt
  - Review continues
- Changes Being Effected (CBE)
  - moderate potential
  - Distribute product upon supplement receipt
  - Review continues

Post Approval Reporting Categories

- Annual Report (AR)
  - » minimal potential
  - » release product upon completion of study

3.2.R. Regional Information Comparability Protocol (U.S. only)

- Location for submission of comparability protocol for post-approval changes (e.g., new WCB qualification, product stability protocol, establishing new lot of reference standard, specific process optimization)
- *Regulatory Mechanism* to demonstrate "...the lack of adverse effect for a specified type of manufacturing change…"
  - Detailed description of proposed change(s)
  - Specific tests, methods, and studies to be performed
  - Acceptable results to be achieved
- May result in reduced reporting category and expedited product distribution

Contract Manufacturing

License Holder

IND
BLA

FDA

Contractor

Contract Quality Agreement

Master File

Principles of Contract Manufacturing

- Regardless of the party performing a manufacturing step, adequate control over manufacturing is maintained
- Ultimately the applicant is responsible for all manufacturing, testing, and quality aspects of the product *(Not out of sight, out of mind)*
- There should be lot-to-lot consistency of the manufacturing product though a controlled process, regardless of the site of manufacture

Contract Manufacturing Applicant Responsibilities

- Manufacture of product complies with license application provisions, and applicable regulations
- Compliance for the contract site with applicable product and establishment standards, including:
  - Biological Product Deviation Reporting, adverse event reporting, product complaints
  - Quality Control as relates to production process
  - Reporting changes to the process and facilities [21 CFR 601.12]

Determining Responsibilities for Contract Manufacturing

Who is responsible???

Applicant

Contractor

FDA

Defining the Responsibilities: A Quality Agreement

- Need to clearly define the responsibilities of each party (written Quality Agreement)
- Define
  - what information will be shared (e.g., changes, new products (multiproduct facility) compliance issues)
  - how information will be shared

Defining the Responsibilities: A Quality Agreement

- Should be documentation to clearly define the responsibilities of both parties, which would address all aspects of manufacturing, record keeping, and communication.
- Company procedures should be compatible with defined responsibilities in the agreement.
- Don’t assume items will be appropriately handled. If the agreement isn’t specific, the responsibilities may not be defined, and problems may result.

Quality Agreements (A short list)

- Clarifies and documents the expectations and responsibilities
- Validation responsibilities
- Documentation review and approval
- Testing and release responsibilities
- Samples and documentation (records)
- Deviations and investigations
- Should protects both parties

Master Files
(the good, the bad and the ugly)

- Submission of information to FDA
  - Permit MF holder to incorporate information by reference when holder submits an IND/ BLA to FDA
  - Permit MF holder to authorize persons to rely on information to support a submission to FDA without the holder disclosing the information to the person
- MF considered confidential by FDA
- Time saving, efficient, can facilitate review – can be win:win:win
- Can result in delays and roadblocks
- The regulations governing Master Files are found at 21 CFR 314.420

Master Files*

- Ordinarily, master files are not independently reviewed - reviewed in context with a specific IND/ BLA
  - What may be acceptable for one product may not be acceptable for another
- Letters submitted in IND/ BLA and master file authorizing reference
- Generally, master files are <u>not appropriate</u> for product - specific information
  - Appropriate (e.g., products manufactured, test procedures, containers and closures)
- *Governed by 21 CFR 314.420

Summary

- CBER - Flexible regulatory approach
  - Different information (type and extent) is sometimes necessary for addressing specific IND CMC issues for different biologic product classes and even individual products within a class
- Newer therapies/ technologies generally result in a greater number and different hold/ product development issues than more established biologics
- Sponsors with minimal regulatory experience & product/ process understanding generally experience greater delays in product approval
- Elements of cGMP need to be in place before Pha 1

Suggestions

- “Know thy process and thy product”
- Reserve sufficient DS & DP retain samples
- Document everything! (integral part of cGMP’s)
- Consult CBER guidance (not a be all/ end all)
- Take advantage of the opportunity to interact with CBER
- Listen and respond to CBER’s comments
- Pay attention to CBER’s non-hold CMC comments for further development
- Continue to partner throughout development, approval, post approval especially with new products and emerging technology

Acknowledgements/Contacts

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Jay Slater, M.D.

Division of Bacterial Products and Allergenic Products, OVRR, CBER (Allergenics)

References

INDs

- The regulations governing INDs are found at 21CFR 312 and those specific to CMC content are in section 312.23(a)(7).
- Guidance Documents on the CBER Website:

  - Guidance for Industry: Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products
  - Draft Guidance for Industry: INDs for Phase 2 and 3 Studies of Drugs, Including Specified Therapeutic Biotechnology-Derived Products, Chemistry Manufacturing and Controls Content and Format
  - Guidance for Industry: IND Meetings for Human Drugs and Biologics; Chemistry, Manufacturing and Controls Information

IDEs

- The regulations governing IDEs are found at 21CFR812 and those specific to CMC content are in section 812.20 (b)(3) & 820.70-75.

- Guidance Documents on the FDA Website:
  - Guidance on IDE Policies and Procedures (CDRH)

Guidance (IND)

- Guidance for Industry: Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products

  Draft Guidance for Industry: INDs for Phase 2 and 3 Studies of Drugs, Including Specified Therapeutic Biotechnology-Derived Products, Chemistry Manufacturing and Controls Content and Format

  Guidance for Industry: IND Meetings for Human Drugs and Biologics; Chemistry, Manufacturing and Controls Information

ICH Quality Guidance

- Applicable to Specified Biologics (May be applicable to other biologics)
  - Q5A: Viral safety evaluation
  - Q5B: Genetic stability of construct
  - Q5C: Stability testing DS/ DP
  - Q5D: Cell substrates
  - Q6B: Specifications
- Generally Applicable to Specified Biologics (May be applicable to other biologics)
  - Q2A & Q2B Analytical Validation
  - Q1AR Stability testing
  - Q1C Photostabiltiy testing
  - Q1E Evaluation of Stability Data (Step4)

Guidance (BLA)

- Guidance for Industry For the Submission of Chemistry, Manufacturing and Controls and Establishment Description Information for Human Blood and Blood Components Intended for Transfusion or for Further Manufacture and For the Completion of the Form FDA 356h "Application to Market a New Drug, Biologic or an Antibiotic Drug for Human Use" (**5/10/1999**)
- Guidance for Industry On the Content and Format of Chemistry, Manufacturing and Controls Information and Establishment Description Information for an Allergenic Extract or Allergen Patch Test (**4/23/1999)**

Guidance (BLA)

- Guidance for Industry: Content and Format of Chemistry, Manufacturing and Controls Information and Establishment Description Information for a Biological In Vitro Diagnostic Product (**3/8/1999)**
- Guidance for Industry: For the Submission of Chemistry, Manufacturing and Controls and Establishment Description Information for Human Plasma-Derived Biological Products, Animal Plasma or Serum-Derived Products (**2/17/1999)**
- Guidance for Industry: Content and Format of Chemistry, Manufacturing and Controls Information and Establishment Description Information for a Vaccine or Related Product (**1/5/1999)**